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Award Number: W81XWH-11-1-0362

TITLE: Whole Brain Networks for Treatment for Epilepsy

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REPORT DATE: July 2012

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01-07-2012	Annual	1 Jul 2011 - 30 Jun 2012

4. TITLE AND SUBTITLE
Whole Brain Networks for Treatment of Epilepsy

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-11-1-0362

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The Cleveland Clinic Foundation

Cleveland, OH 44195-0002

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The most significant finding during this research period was a clear theoretical foundation for partial differential equation (PDE)-based tractography that inherently includes constraints within the formalism. This foundation has enabled us to make rational choices in developing an algorithm capable of mapping whole-brain networks of axonal connectivity. The algorithm satisfies two necessary conditions: 1) it can identify connections invisible to standard streamline throughout the entire brain and 2) it is fast enough for practical use. Although correlation with gold-standard electrophysiology measurements of connectivity is weak, the developed formalism will make it practical to incorporate information from other imaging modalities with the long range goal of developing a noninvasive biomarker for traumatic brain injury-related epilepsy.

15. SUBJECT TERMS
Traumatic Brain Injury. Epilepsy. Tractography. Electrophysiology. Connectivity.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
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INTRODUCTION

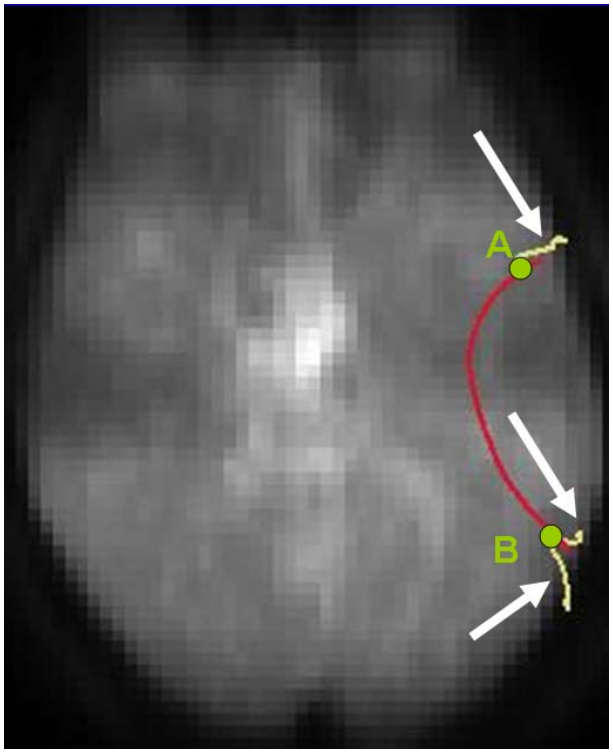

Figure 1. Failure of deterministic tracking for application to intracranial electrodes. Deterministic tracks (pale yellow lines, indicated by arrows) originating in cortical regions (A, B) fail to connect the cortical regions. PDE-generated track (red line) readily delineates connection.

This project addressed the FY10 PRMRP *subject* of epilepsy. Increasing incidence of traumatic brain injury (TBI) among soldiers will likely lead to elevated levels of disability due to TBI-related seizures and epilepsy. The lack of a reliable biomarker hinders efforts to interrupt the evolution of epilepsy from TBI. A new, network paradigm for analysis of brain imaging data suggests a new direction for diagnosing brain injury. Existing analyses have neither been applied to epilepsy nor have been validated by gold standard data. The *purpose* of this research was to initiate exploration of the concept that network properties of imaging data within the *scope* of predicting the transition of TBI to epilepsy. The specific objectives of this project were to develop a fast analysis protocol and validate the analysis with gold-standard invasive electrophysiology measurements from epilepsy patients. The innovative aspects of the research are application of a partial differential equation framework for fast analysis, the application of the network paradigm to epilepsy patients and validation with gold standard invasive measurements. The relevance of the project to the FY10 PRMRP topic of epilepsy stems from the potential use of a validated, network paradigm as a biomarker of risk for the transition from TBI to epilepsy with the intent of interrupting that transition.

BODY

Research accomplishments are summarized below along the lines of The Statement of Work, which outlined the following main tasks:

- Develop a partial differential equation (PDE)-based tractography methodology to enable fast, whole-brain measurements of connectivity.
- Validate noninvasive measurements of connectivity by comparison to gold standard, invasive electrophysiology measurements.
- Summarize and publish results.

Develop a partial differential equation (PDE)-based tractography methodology to enable fast, whole-brain measurements of connectivity.

A principled theoretical framework for PDE-based tractography was developed and presented at the 2012 IEEE Workshop on Mathematical Methods in Biomedical Image Analysis (1) and the 2012 Scientific Meeting of the International Society for Magnetic Resonance in Medicine (2). Details of the theory and fast implementation are included in the attached publication (1). Highlights include:

- For the first time, encoding of termination constraints on the PDE tractography within the formalism itself as opposed to ad-hoc filtering.
- Acceleration over standard probabilistic tracking by several orders of magnitude from, for example 10 cpu-hours for a single track with standard approaches to 2 cpu-*seconds* with the new approach.
- The acceleration of the implementation over standard approaches will enable whole-brain tractography.

An important feature of the new approach is that it successfully delineates tracks when standard tractography fails (figure 1).

Validate noninvasive measurements of connectivity by comparison to gold standard, invasive electrophysiology measurements.

A total of 5 subjects's imaging and electrophysiologic data were examined. Although we originally proposed examining data from 10 subjects, electrophysiologic data were incomplete in all but 5.

The overall strategy is to compare measures of anatomical connectivity from tractography with gold standard measures of connectivity from electrophysiology. Figure 2 indicates the location of subdural electrodes in one subject. Connectivity is measured by first identifying Broca's area on the grid with a speech arrest task (electrodes 11 and 12 on figure 2). Cortico-cortico evoked potentials (CCEP) are measured between these and all other electrodes to identify points of highest connectivity.

The new PDE-based methodology was able to identify connections between any given pair of electrodes in all subjects examined (figure 3). A sagittal view of the brain with overlaid tracts derived from the fast PDE methodology is shown in figure 4. The seed point for all tracts is in the Broca's region of the left inferior frontal gyrus. The target points are electrode contact points of subdural grids overlaid on the left parietal and temporal lobes. As emphasized by the color coding, the tracts can be grouped into three bundles, which correspond to known physiology: the red tracts show the cluster connecting Broca's region to the presumed Wernike's region of the left temporal-parietal lobes along the superior longitudinal fasciculus, particularly the arcuate fasciculus. The blue tracts fan out across the external capsule to connect to the superior and middle temporal gyrus. The green tracts are bundled along portions of the left uncinate fasciculus.

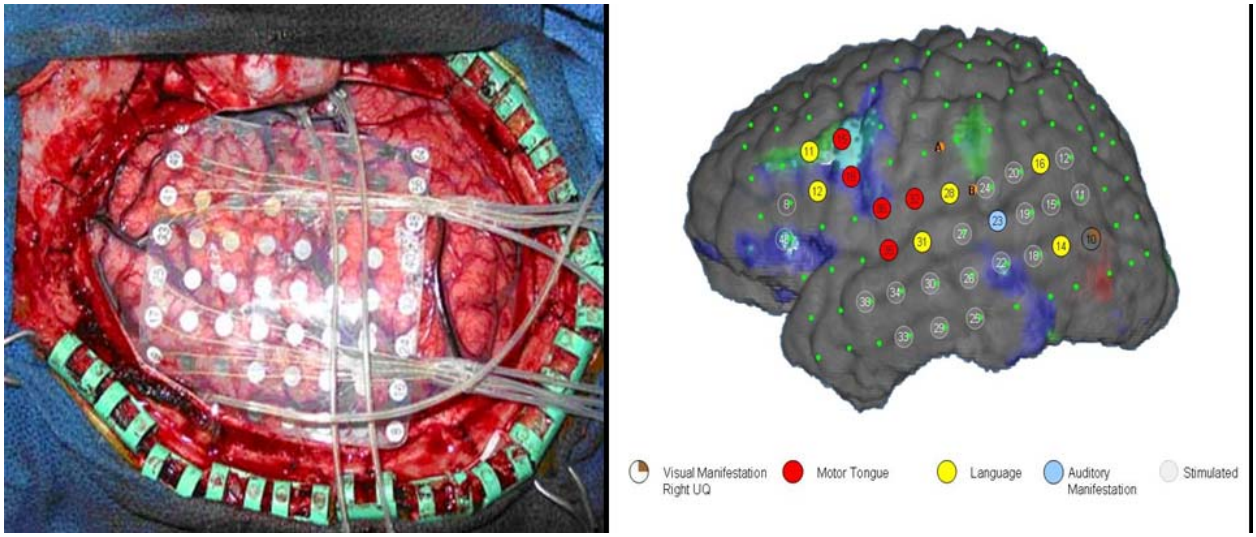

Figure 2. Photograph of subdural electrodes (left) and functional maps derived from electrical stimulation (right).

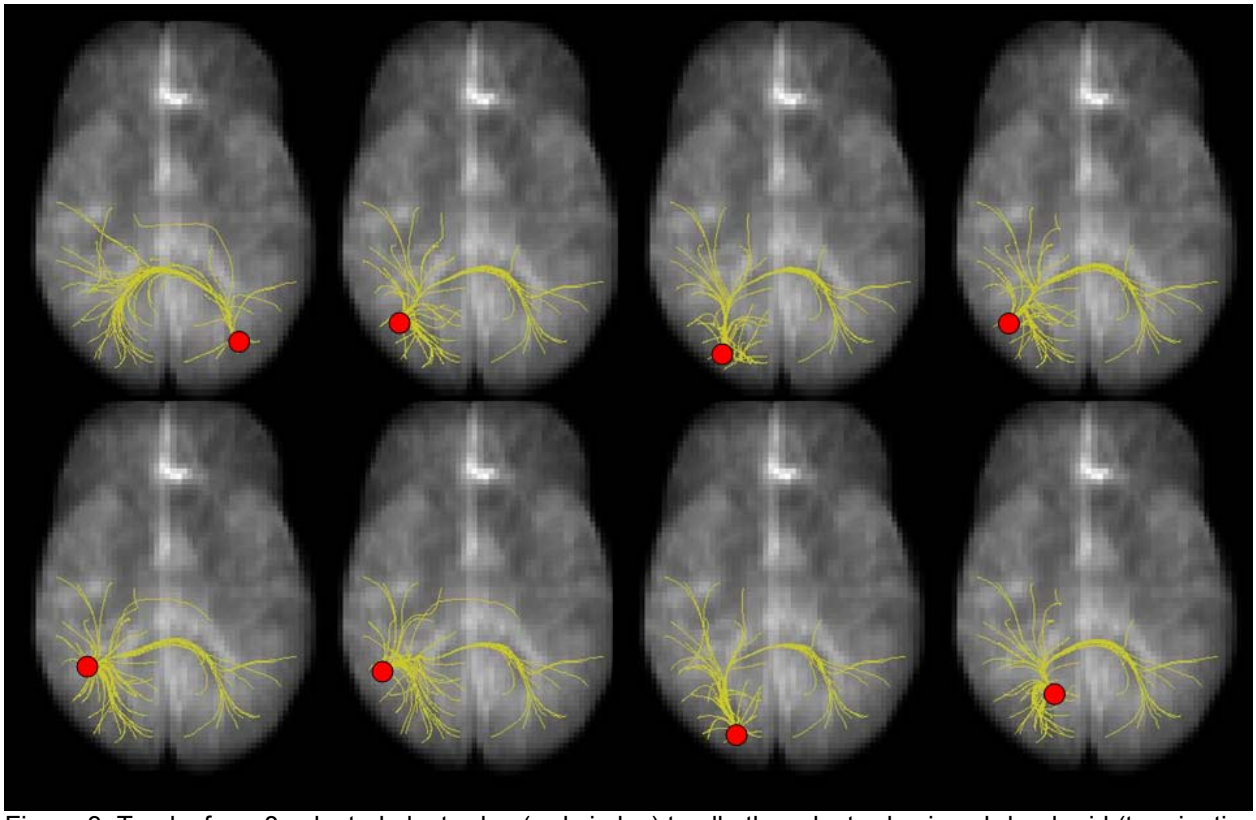

Figure 3. Tracks from 8 selected electrodes (red circles) to all other electrodes in subdural grid (terminations of yellow lines).

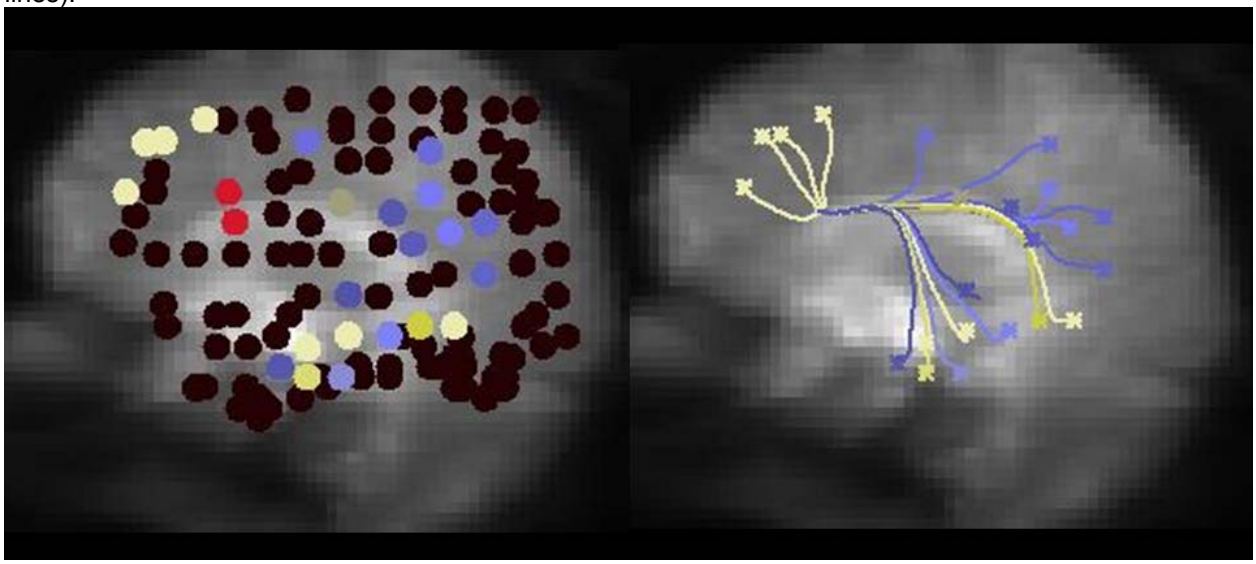

Figure 4. Sagittal view of the brain with overlaid tracts derived from the fast PDE methodology

Correlation with electrode measures of connectivity, however, was modest. Figure 5 shows a two dimensional scatter-plot comparing electrophysiological (EP) connectivity vs DWI connectivity, in an epilepsy patient with left-sided subdural grids. Paired electrode contacts overlaying Broca's region in the left inferior frontal gyrus were stimulated using a CCEP protocol (8 mA, 1 Hz, alternating unipolar pulse with 0.3 msec duration). Recordings were made over 92 grid contacts placed over the left parietal and temporal lobes. Tractography was performed using the fast PDE approach between the Broca's contact and all remaing electrodes, for a total of 92 tracts. The connectivity of each track was scored in a measure reflecting tract-density, and these values are scored along the x-axis. The y-axis shows the magnitude of the electrophysiological response between 10-20 msec after the stimulus. A modest correlation is seen ($r=0.45$), many contacts show either a strong EP connectivity with a poor DWI connectivity, or a poor EP connectivity with a strong DWI connectivity. Furthermore, the correlation does not achieve statistical significance ($p > 0.2$).

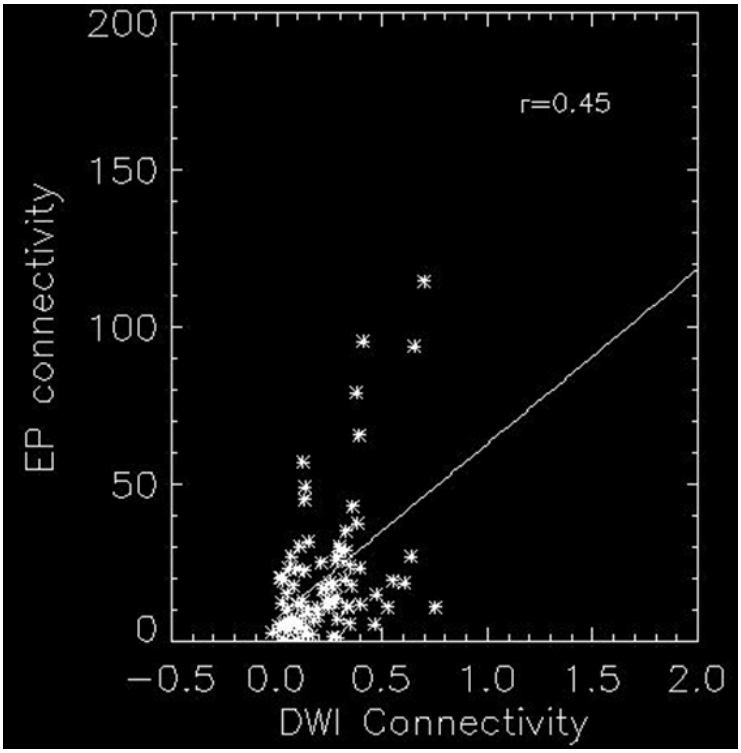

Figure 5. Correlation between Tractography-based and electrophysiologic connectivity.

This result, presented at the 2012 scientific meeting of the American Society of Neuroradiology (3), indicates that the link between electrophysiologic and anatomical connectivity is not strong. Competing hypotheses for the weak correlation include:

1. Assuming that tractography identifies true axonal connections, electrophysiologic connections may proceed over other, less direct routes.
2. The weak correlation may indicate the limits to reliability of tractography-based delination of axonal connections.
3. Coregistration of electrode locations to image positions is hampered by brain shift and the absence of post-implantation images.

The first two items may be addressed by direct examination of white matter pathways on pathology from surgically resected tissue. In this way, it may be possible to independently test if tractography identifies white matter connections. Also, the presence of an anatomical connection does not ensure the presence of electrical activity along that pathway. Future work will involve the use of functional connectivity measurements (4, 5) to incorporate measurements of activity. The coregistration issue may be addressed by taking advantage of newly developed stereotactically implanted electrodes (figure 6) which obviate brain shift and in which electrode location can be known to the limit of the accuracy of the stereotactic frame.

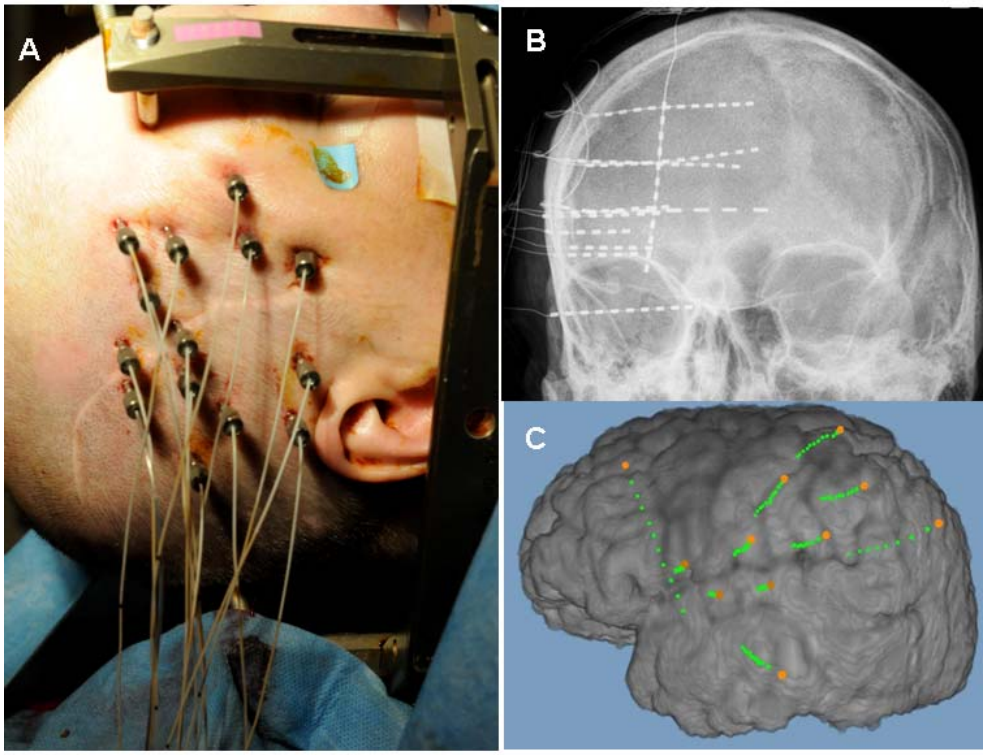

Figure 6. Stereotactically implanted electrodes (A) do not lead to brain shift found in subdural electrodes (figure 6) because the skull is left intact. Location of electrodes and also be determined to high precision after implanation (B,C).

Summarize and publish results.

Work described here has been presented at 3 international meetings (1-3). Manuscripts are currently in preparation describing the theory and implementation of the tractography and of correlation with electrode recordings.

KEY RESEARCH ACCOMPLISHMENTS

- Development of a theoretical basis for PDE-based tractography.
- Implementation of the tractography that is fast enough to enable whole-brain tractography.
- Finding of weak correlation between gold-standard electrode recordings and anatomical connectivity based on tractography.

REPORTABLE OUTCOMES

- Presentation at 2012 IEEE Workshop on Mathematical Methods in Biomedical Image Analysis (1).
- Presentation at the 2012 Scientific Meeting of the International Society for Magnetic Resonance in Medicine (2)..
- Presentation at 2012 scientific meeting of the American Society of Neuroradiology (3)

CONCLUSION

We have implemented a methodology for tractography that is fast and able to assess connections throughout the entire brain. This methodology promises to enable whole-brain assessment of networks of brain connections. The correspondence between these connections and electrophysiologic activity is not simply one-to-one. This limitation may be addressed by including other imaging measures, such as functional connectivity, and other ground-truth measurements such as stereotactic recordings and myelin stains of ex-vivo tissue.

As a scientific or medical product, the work accomplished represents a step towards totally non-invasive evaluation of the brain at risk for epilepsy. Such an evaluation would enable rapid evaluation of pharmacologic interventions and development of new therapies. Unfortunately, although victims of traumatic brain injury are at high risk for developing epilepsy, there is no clear-cut way to predict or evaluate strategies for treating epileptic seizures. On the near term, surgical intervention for phamacoresistant epilepsy often relies on highly invasive electrode monitoring that is an option for only the most highly motivated patients. Progress toward noninvasive detection of targets for surgical resection would relieve the burden of suffering among these patients while opening up new treatment options.

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Toward Whole-Brain Maps of Neural Connections: Logical Framework and Fast Implementation

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Abstract

MRI tractography is the only method that noninvasively maps neural connections in the brain. Interest in its use for diagnosis and treatment of neurological disease is growing rapidly. Probabilistic tractography provides quantitative measures that can be interpreted as the strength or reliability of connections, but Monte Carlo implementations can require impractical computation times and have difficulty identifying connections between distal regions. Here, we develop a generic logical framework for probabilistic tractography with minimal assumptions that lends itself to solution by standard finite-difference methods. We demonstrate an implementation that outperforms Monte Carlo approaches in terms of computation time and identifying distal connections. The generality of the logic and the speed of the implementation indicate the potential of this approach for real-time mapping of whole-brain neural connections.

1. Introduction

Accurate, noninvasive maps of neural connections in the brain have the enormous potential to improve diagnosis and treatment of neurological disease. For example, neurosurgical treatment for medically refractory epilepsy requires identification of regions of abnormal electrical activity in the brain for resection. Implanted electrodes used for this purpose are limited in size and can therefore miss the target while imposing risk from their invasive nature. A compelling rationale for tractography is to augment or even replace such invasive procedures. By providing noninvasive, whole-brain maps of neural connections, tractography may be able to identify targets for resection that the electrodes miss.

Unfortunately, tractography in its current state cannot provide reliable whole-brain maps for practical use. Standard deterministic tractography [1-3] misses many known connections [4]. Probabilistic tractography identifies additional connections [5] but can require computational times that are too long to impact treatment. More important, tractography can generate false connections. Statistical methods, based on probabilistic tractography for filtering these false connections, are promising [6, 7] but incur additional computational burden.

In this paper, we develop a generic logical framework for widespread tractography that lends itself to a fast numerical implementation. By taking into account a minimal set of logical conditions, it is possible to use the rules of probability theory to construct a solution for the density of tracks in every voxel. The solution lends itself to fast numerical solution by finite difference methods, such as simultaneous over-relaxation or conjugate gradient algorithms [8]. We show such implementations offer orders-of-magnitude speed advantage over more standard Monte Carlo implementations of probabilistic tractography, particularly in geometries challenging to the latter.

2. Theory

Our objective is to count the number of fiber tracks in each voxel subject to the conditions that all tracks start in a given seed voxel and all terminate in a given target voxel, without crossing given boundaries. For example, the superior part of the corticospinal tract can be identified by generating fiber tracks seeded in the posterior limb of the internal capsule and terminating in the motor cortex. Note that "trac*t*s" refer to anatomical nerve pathways while "trac*k*s" refer to the mathematical curves generated by tractography algorithms.

We begin by defining a quantity that will be shown to be equivalent to the desired track count:

> $\varphi(j) \equiv$ "the number of tracks originating in voxel j subject to the condition that the tracks reach the target voxel before hitting either the seed voxel or boundary region." Note that $\varphi(j)$ forms a subset of all tracks leaving j; that is, of all tracks originating from j, many hit the boundary or return to the seed before hitting the target.

The originating voxel may be set as the seed voxel. Furthermore, sets of seed or target voxels can be considered instead of individual voxels. For the sake of brevity, the condition will be referred to as "reaching the target."

The assumption that tracks are conserved leads to the solution for $\varphi(j)$. The assumption simply states that tracks neither appear nor disappear at any points but the seed, target or boundary. A consequence of this assumption is that the value of $\varphi(j)$ is directly related to the value of $\varphi(i)$ at all neighbor voxels, i:

$$\varphi(j) = \sum_i p(i,j)\varphi(i) \tag{1}$$

where $p(i,j)$ is the probability that a track moves from i to j, subject to the condition that it reaches the target. If we assume that the tractography is a Markov process (has no memory), $\varphi(j)$ is not only the number of tracks that *originate* in j, subject to the conditions, but is also the number of tracks *in* j, the desired quantity. Solving for $\varphi(j)$ will therefore achieve our objective. Achieving the solution has two components: the *logical* task of deriving the probabilities, $p(i,j)$, and the *numerical* task of calculating the values of $\varphi(j)$ once the $p(i,j)$ have been derived.

The logical task of relating $p(i,j)$ hinges on its definition as a *conditional probability*. The condition that tracks reach the target can be encoded directly into the probabilities:

$$p(i,j) = \frac{p(A \cap B)}{p(B)} \tag{2}$$

where B is the proposition, "track reaches the target" and A is the proposition, "track moves from i to j." We define $\lambda(i,j)$ as the probability of the track moving from i to j and $r(j)$ as the probability that a track originating in j reaches the target. Assuming the independence of $\lambda(i,j)$ and $r(j)$, the joint probability of the track moving from i to j and then proceeding to the target is:

$$p(A \cap B) = \lambda(i,j)r(j) \tag{3}$$

while the overall probability of reaching the target from the originating voxel, i, is $r(i)$. We therefore find:

$$p(i,j) = \frac{\lambda(i,j)r(j)}{r(i)} \tag{4}$$

Figure 1 diagrams a concrete example illustrating the intuition behind equation 4.

Although the probability, $r(j)$, is distinct from the previously defined quantity, $\varphi(j)$, which is the *number* of tracks in j, we can use a similar conservation argument to construct a solution:

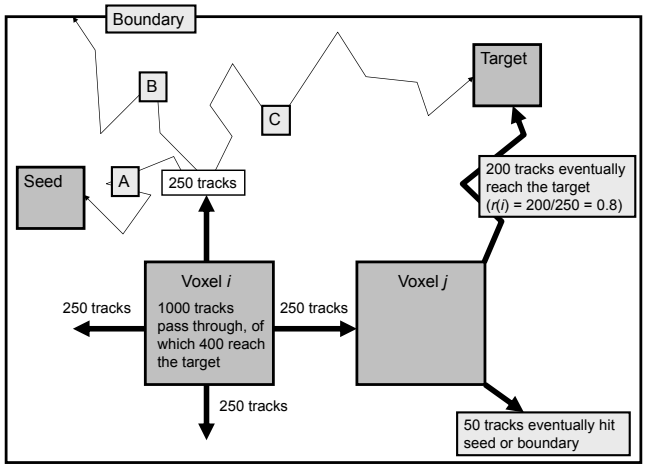


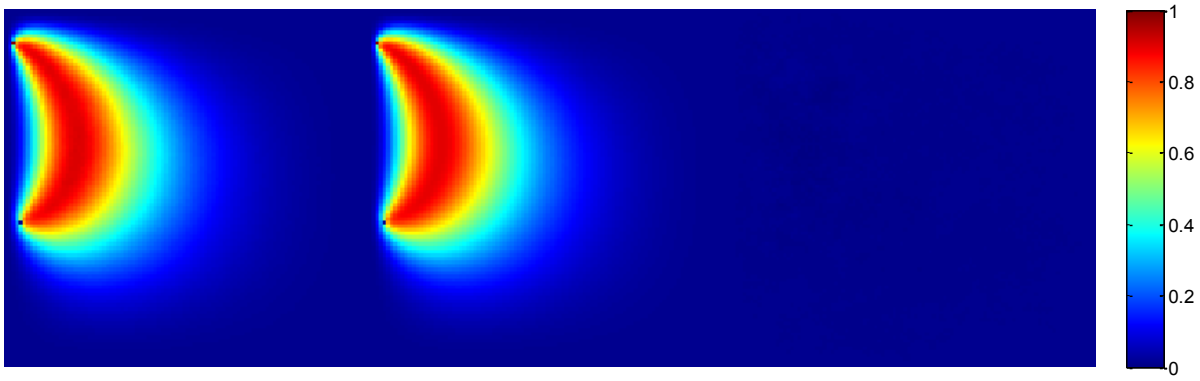
Figure 1: Cartoon example showing application of conditional probabilities. Consider 1000 tracts originating from voxel i. Of these, only a fraction (40% in this example, or $r(i) = 0.4$) reach the target voxel (for example, track "C"), with many tracts hitting either the boundary ("B") or returning to the seed ("A"). In this 2-D example, there is a 25% probability for each tract to step into one of the four orthogonal directions ($\lambda(i,j) = 0.25$ is constant). Consider those tracts that step into the adjacent voxel j. Of those, 200 reach the target (i.e. $r(j) = 200/250 = 0.8$). We can thus see that the probability for a successful track to reach the target from i via j is $p(i,j) = 200/400 = (1000 \times 0.25 \times 0.8)/(1000 \times 0.4) = \lambda(i,j) \times r(j)/r(i)$.

$$r(i) = \sum_j \lambda(i,j)r(j) \tag{5}$$

The probability that a track originating in i reaches the target is the sum of the probabilities that the track moves to neighbors j, each multiplied by the probability of tracks originating in j reaching the target. This simply uses the fact that if i is not the target, any track must pass through some neighbor before reaching the target.

As $\lambda(i,j)$ indicates the likelihood that a track moves from i to j regardless of any other conditions, it is an entirely *local* property. This quantity can be estimated from the data. For example, previous work has derived a similar quantity by integrating a function of the diffusion tensor over a solid angle around a line connecting neighboring voxels [9]. Alternatively, integration can be implemented over a function that accounts for complex fiber geometries, such as the diffusion or fiber orientation distribution function (dODF or fODF, respectively) [10, 11].

The logical derivation is now complete. From the data, we derive the local probability, λ, which, through equation 5, allows us to derive the probability r. The probabilities p follow through equation 4, leading to the desired quantity, φ.



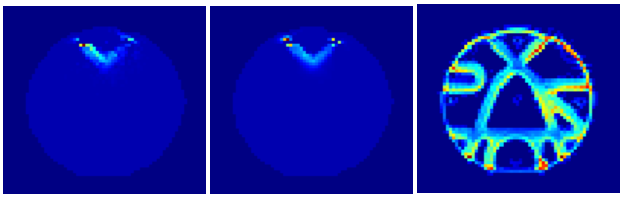


Figure 3: Corrected track densities in the hardware phantom using the Monte Carlo (left) and the finite difference approaches (center), which required 60 hours and less than 1 second, respectively. A fractional anisotropy map (right) is shown for reference.

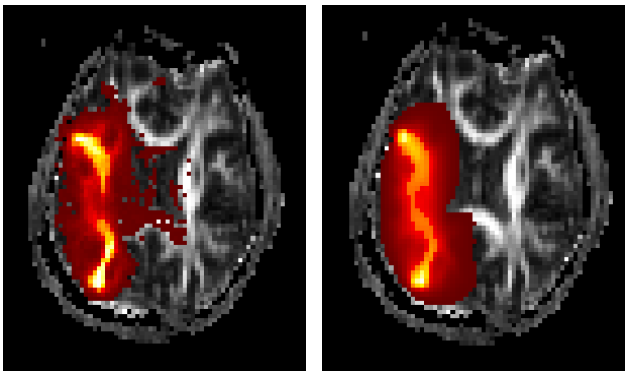


Figure 4: Corrected track densities calculated by the Monte Carlo (left) and finite-difference (right) approaches, overlaid on fractional anisotropy maps for anatomical reference.

the seed, r is set to 0 at the seed. The number of tracks, φ, can be set to an arbitrary value at the seed and is set to 0 at the boundary. In order to avoid the target acting as a source of tracks, φ must be set to 0 at the target. For the numerical approach, we applied both a simultaneous over-relaxation method (e.g. Gauss-Seidel) and a biconjugate gradient stabilized method. The latter recasts each finite difference equation into a massive, but sparse, matrix equation.

3. Methods

Solutions were implemented in IDL (ITT Visual Information Systems, Boulder, CO) and MATLAB (The Mathworks, Natick, MA). Test data sets were used to compare this solution with a Monte Carlo probabilistic tractography routine [12]. The latter is essentially a weighted random walk, in which the probability of stepping in a given direction is determined from underlying diffusion imaging data. The test data sets included numerically synthesized phantoms, a hardware phantom from the fibre cup competition [13] and *in vivo* data. The *in vivo* data was acquired under a protocol approved by the Cleveland Clinic Institutional Review Board. Whole-brain high angular resolution diffusion imaging (2.5 mm isotropic voxels, 61 non-collinear diffusion-weighting gradients with b=1000sec/mm^2 and 7 b=0 acquisitions) was acquired on a Siemens TIM Trio (Siemens Medical Solutions, Erlangen) followed by iterative motion correction [14]. For the hardware phantom and *in vivo* data, fODFs were calculated in each voxel by spherical deconvolution [10] with user-independent optimized regularization [15]. Local hopping probabilities, λ, were calculated by integrating over the solid angle of a vector connecting each voxel with its 26 neighbors. In the numerical phantoms, the probabilities were set directly. For each test data set, the solution was also found assuming isotropic probabilities.

4. Results

A configuration in which a seed and target are near the boundary, such as those found in proximal cortico-cortico U-fiber connections, is particularly difficult for the Monte Carlo approach, but not for the finite-difference implementation. Figure 2 shows an illustration via a numerical phantom, a simple 2-dimensional region with isotropic probabilities. Seed and target voxels were placed near the boundary. Track counts were normalized to the value set at the seed, yielding a normalized track density. While the Monte Carlo and finite difference approaches yielded track densities that differed by no more than 2%, the finite difference was faster by four orders of magnitude.

Figure 3 shows results from the fibre cup hardware phantom. A simple correction was implemented in order to account for chance connections associated with probabilistic tractography. Track densities calculated assuming isotropic hop probabilities, λ, were subtracted from those calculated using probabilities derived from the fODF. This correction has been developed more fully in the Monte Carlo framework [6]. Although the Monte Carlo approach required over 60 hours and the finite difference approach required less than 1 second, the latter resulted in a smoother map.

In vivo data is shown in Figure 4. While the Monte Carlo approach required 10 hours of computation, the finite difference approach required only 2 seconds. The huge difference in computation time results partly from the difficulty with which the Monte Carlo approach is able to determine track densities at regions distal to the seed. Much iteration is required by the Monte Carlo method, while the finite difference approach converges rapidly and at the same rate at proximal and distal sites.

5. Discussion

We demonstrate that a minimal set of assumptions and logical considerations can lead to a fast solution for tractography. Most previous probabilistic approaches [16, 17] considered only the local probability, λ, of moving between neighboring voxels. A Bayesian approach by Friman et al. [18] considered conditional probabilities, but with more specific conditions associated with the trajectory of each track, particularly as influenced by boundaries

A number of issues remain to be resolved. Optimal calculation of the local probability may depend on the choice of dODF or fODF, of which there are many types [19]. Other numerical solutions may yield even greater performance benefits. Also, the correction approach using subtraction of isotropic track densities is ad-hoc and not as well-developed as that derived in the context of Monte Carlo approaches [6].

6. Conclusion

The proposed method yields results comparable to more standard Monte Carlo approaches to probabilistic tractography. However, the enormous boost in speed suggests the possibility of determining whole-brain anatomical connectivity in a clinically relevant amount of time.

Acknowledgements. We gratefully acknowledge support from DOD USAMRAA PR100438, Neuroradiology Education Foundation NREF1004SJ and the Summer on the Cuyahoga internship program.

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